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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,094	12/31/2003	Gautam Vinod Daftary	2912960-001000	6940

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EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
10/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/748,094	DAFTARY ET AL.	
	Examiner	Art Unit	
	GOLLAMUDI S. KISHORE	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,12,14-22 and 63-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,12,14-22 and 63-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of applicant's priority papers dating back to 12-31-2002, the references of Wong and Mammarella are removed from the rejections and the prosecution is reopened.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 69 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by "at least 25 times longer than conventional ***non-liposomal*** formulations when tested in Swiss albino mice at equivalent doses. When a liposomal formulation is tested with a ***non-liposomal formulation***, it is natural for the liposome formulation to have a longer circulation times because liposomes are sustained release vehicles. Furthermore, what is being tested? Phospholipid, cholesterol mixture?

Applicant's arguments have been fully considered, but are not persuasive. Applicant points out to page 5 and argues that this expression is defined in the specification. On page 5, applicant states the following: "wherein the non-peglated doxorubicin liposomes have a circulation time in blood at least 25 times longer than that obtained with ADRIAMYCIN when tested in swiss albino rats".

This argument is not persuasive. First of all claim 1 does not recite doxorubicin as the active agent. In fact, claim 1 does not recite any active agent. Secondly,

Adriamycin is a solid and one can make different forms of non-liposomal compositions such as emulsions and even other non-liposomal sustained release formulations.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-8, 10, 12, 14-22 and 63-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong (Clinical Cancer Research, 1999) of record, Janoff (4,880,635) and Papahadjopoulos 4,235,871) optionally in further combination with Barenholz (5,316,771).

Hong teaches a direct comparison of liposomal doxorubicin with or without polyethylene glycol coating. ***According to Hong, "Paradoxically, the group of mice treated with liposomal doxorubicin without PEG had higher tumor doxorubicin concentrations" (Abstract).*** The method of preparation involves the preparation of a lipid film containing DSPC and cholesterol and the hydration of these lipids using ammonium sulfate solutions. Although pH of these solutions is indicated, it is unclear whether buffers are used to prepare the ammonium sulfate solutions in Hong. Doxorubicin was loaded into the liposomes by remote loading (abstract and Materials and Materials and Methods) and therefore, the removal of external ammonium sulfate

for this loading is implicit in Hong. What is also lacking in Hong is the use of sucrose and histidine in the hydration buffer. Also unclear from Hong as to how much hydration buffer is added. However, since to form liposomes sufficient hydration of the lipids is important, it would have been obvious to one of ordinary skill in the art to determine as to how much hydration buffer is needed for complete formation of liposomes.

Papahadjopoulos discloses methods of formation of liposomes. The methods involve either removal of the organic solvent before hydration (Example 1) or making an emulsion using an organic solvent containing phospholipid and an aqueous medium and evaporating the organic solvent (Example 2). In either method, the amount of the lipid is 100 micromoles and the aqueous medium added is 1.5 ml which corresponds to 15 ml of aqueous medium per millimole of the phospholipid.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (Example 1; col. 21, line 23 through col. 21, line 27). Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole).

Barenholz teaches a method of creating an ammonium sulfate gradient in liposomes to load active agents into liposomes. The method involves hydrating the lipid film with ammonium sulfate and removal of the external ammonium sulfate followed by loading of the amphipathic active agent. According to Barenholz, effectively removing the outside ammonium by methods used and recognized in the art, in particular, dilution, gel exclusion, dialysis and diafiltration (abstract, col. 6, lines 10-38, columns 9 and 10 and examples).

It would have been obvious to one of ordinary skill in the art to include sucrose and histidine in Forssen since Janoff teaches that sucrose protects the liposomes during the dehydration/rehydration process and Papahadjopoulos teaches the routine practice of the inclusion of histidine in the hydration buffer. The removal of external ammonium ions by dialysis in Hong would have been obvious to one of ordinary skill in the art since such a removal results in the formation of ammonium gradient for the subsequent loading of active agents as taught by Barenholz.

5. Claims 1-8, 10, 12, 14-22, 63-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater (6,355,268) in view of Janoff (6,355,268).

Instant claims are process claims. As pointed out above, instant claim 1 recites two alternatives. One of which is dissolving the phospholipids in a solvent and adding the hydration buffer to the organic solution and removing the organic solvent.

Slater discloses a process of preparation of liposome entrapped topoisomerase inhibitors. The process involves dissolving phospholipids and cholesterol in ethanol, adding an aqueous medium containing ammonium sulfate. The ammonium sulfate and ethanol were removed from the external bulk aqueous phase immediately prior to remote loading of the active agent by hollow fiber tangential flow diafiltration. The liposomes were then mixed with the drug solution containing 10 % sucrose solution. The unencapsulated drug in the bulk phase is then removed by diafiltration using exchange buffer containing 10 % sucrose and 10 millimolar Histidine, pH 6.5.
What is lacking in Slater is the inclusion of sucrose and buffer in the hydrating medium.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (col. 2, line 19; col. 21, line 23 through col. 21, line 27). The phospholipids are dissolved in chloroform, evaporating chloroform and hydrating the phospholipid with a hydrating medium containing the protective sugar and a buffer. Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole) (col. 4, lines 55-66, col. 8, lines 31-47 and Example 1).

It would have been obvious to one of ordinary skill in the art to include sucrose in the hydrating medium of Slater since Janoff teaches that sucrose enables the liposomes to retain the active agent. The use of Histidine as the buffer along with the ammonium sulfate and sucrose would have been obvious to one of ordinary skill in the art since Janoff teaches the inclusion of a buffer and Slater teaches the use of this buffer in the final liposomal preparation. Although in the method of preparation, Slater uses topoisomerase inhibitors, one of ordinary skill in the art would be motivated to use any active agent with a reasonable expectation of success. Although Slater uses a polymer containing phospholipid in the preparation of liposomes, one of ordinary skill in the art would be motivated to prepare liposomes without polymer-phospholipid since Janoff teaches that liposomes can be prepared without the use of polymer-phospholipid. Slater does not teach the encapsulation of active agents other than topoisomerase inhibitors. However, since liposomes are known to encapsulate a variety of active agents, it would have been obvious to encapsulate any active agent with a reasonable expectation of success.

6. Claims 1-8, 10, 12, 14-22 and 63-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forssen (5,714,163) in combination with Janoff (4,880,635) and Papahadjopoulos (4,235, 871), optionally in further combination with (Slater (6,355,268) and/or Clerc (5,939,096).

Instant claims recite two alternatives: the organic solvent is removed before or after the hydration. That means the hydration is performed on a dried lipid film or in a solution of the lipids in the organic solvent.

Forssen discloses a method of preparation of liposomes wherein the spray dried lipid mixture containing DSPC and cholesterol is hydrated with ammonium sulfate. Since it is a lipid mixture dissolving the lipids in an organic solvent for spray-drying is implicit (Example 1). Although Forssen teaches the use of 300 mM sucrose for hydration medium, he does not teach the use of hydration buffer containing both ammonium sulfate and sucrose. It is unclear whether in Forssen, the hydrating sucrose solution is in a buffer. The liposomes in Forssen are then subjected to buffer change using 300 mM sucrose. The removal of ammonium sulfate in this step thus, is implicit in Forssen.

Forssen however, does not teach the hydration of the lipid using ammonium sulfate, Sucrose and histidine.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (col. 2, line 19; col. 21, line 23 through col. 21, line 27). The phospholipids

are dissolved in chloroform, evaporating chloroform and hydrating the phospholipid with a hydrating medium containing the protective sugar and a buffer. Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole) (col. 4, lines 55-66, col. 8, lines 31-47 and Example 1).

Papahadjopoulos discloses methods of formation of liposomes. The methods involve either removal of the organic solvent before hydration (Example 1) or making an emulsion using an organic solvent containing phospholipid and an aqueous medium and evaporating the organic solvent (Example 2). In either method, the amount of the lipid is 100 micromoles and the aqueous medium added is 1.5 ml which corresponds to 15 ml of aqueous medium per millimole of the phospholipid and the hydration medium contains histidine.

Slater discloses a process of preparation of liposome entrapped topoisomerase inhibitors. The process involves dissolving phospholipids and cholesterol in ethanol, adding an aqueous medium containing ammonium sulfate. The ammonium sulfate and ethanol were removed from the external bulk aqueous phase immediately prior to remote loading of the active agent by hollow fiber tangential flow diafiltration. The liposomes were then mixed with the drug solution containing 10 % sucrose solution. The unencapsulated drug in the bulk phase is then removed by diafiltration using exchange buffer containing 10 % sucrose and 10 millimolar Histidine, pH 6.5.
What is lacking in Slater is the inclusion of sucrose and buffer in the hydrating medium.

Clerc while disclosing a drug loading method into the liposomes teaches the hydration of the phospholipids with a solute species which is saline or a disaccharide

(sucrose) and a buffer which is the same as the internal or external aqueous medium such as histidine or MES or Tris (col. 7, lines 5-15; col. 8, lines 1-15).

It would have been obvious to one of ordinary skill in the art to include sucrose and histidine in Forssen since Janoff teaches that sucrose protects the liposomes during the dehydration/rehydration process and Papahadjopoulos teaches the routine practice of the inclusion of histidine in the hydration buffer. One of ordinary skill in the art would be motivated further to include both sucrose and histidine in the hydrating medium since both Slater and Clerc teach the use of this combination in the liposomal preparations.

State of the Art

The references of Uchiyama (International Journal of Pharmaceutics, 1995) and Radhakrishnan (5,192,528) which teach hydration of the lipid film with the claimed amounts of hydration medium are already of record. (see Materials and Methods of liposome preparation of Uchiyama and abstract and col. 5, lines 15-29 of Radhakrishnan. The reference of Kirpotin which teaches hydration of lipid with a buffer containing ammonium sulfate and also 377 mmole sucrose (examples 7 & 8) is also of record.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK